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PATENT SPECIFICATION

NO DRAWINGS

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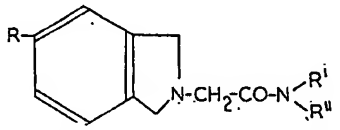
COMPLETE SPECIFICATION

New Amides of Isoindolinyl-2-Acetic Acid

We, VEB ARZNEIMITTELWERK DRESDEN, of 35, Wilhelm-Pieck-Strasse, Radebeul 1, Germany, a Corporation organised under the laws of Eastern Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new amides of isoindolinyl-2-acetic acid and with the preparation thereof.

The new amides according to the present invention are compounds of the general formula:—



wherein R is a hydrogen atom or a primary amine group and R^1 and R^{11}, which may be the same or different, are hydrogen atoms or alkyl radicals or R^1 and R^{11} may be joined together directly or through a hetero atom to form a cyclic radical.

These new compounds are characterised by a good analgesic effect and a considerable period of action, together with a low toxicity.

The amides according to the present invention can be prepared by the reaction of isoindoline or 5-amino-isoindoline with an appropriate haloacetic acid amide in a solvent, the desired compounds being obtained, together with isoindoline hydrohalide or 5-amino-isoindoline hydrohalide.

The compounds of the above-given general formula are, as tertiary amines, too strongly basic to be used as such therapeutically. Consequently, for therapeutic application, they are used in the form of acid addition salts with physiologically acceptable acids.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1.

β-2-Isoindolinyl-acetamide.

2.38 g. (20 mMol) isoindoline are dissolved in 100 ml. dioxan, 0.94 g. (10 mMol) chloroacetamide added thereto and the solution heated under reflux for 2 hours. The hot solution is filtered free of isoindoline hydrochloride (1.37 g. = 88%), evaporated and the residue recrystallised from dioxan. There are thus obtained 1.43 g. (81% of theory) β-2-isoindolinyl-acetamide with a melting point of 210° C.

Analysis: calc. nitrogen content for $C_{10}H_{12}N_2O$: 15.90%
found : 15.87%

EXAMPLE 2.

β-2-Isoindolinyl-acetic acid methylamide.

2.38 g. (20 mMol) isoindoline are dissolved in 150 ml. chloroform, 1.08 g. (10 mMol) chloroacetic acid methylamide are added thereto and the solution heated under reflux for 90 minutes. After cooling, the solution is suction filtered free of isoindoline

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hydrochloride (1.39 g. = 89.5%), the solution evaporated and the residue recrystallised from benzene. There are thus obtained 1.58 g. (83% of theory) β-2-isoindolinyl-acetic acid methylamide with a melting point of 149° C.

Analysis: calc. nitrogen content for $C_{11}H_{14}N_2O$: 14.72%
found : 14.76%

EXAMPLE 3.

β-2-Isoindolinyl-acetic acid pyrrolidide.

2.38 g. (20 mMol) isoindcline are dissolved in 100 ml. dioxan, 1.48 g. (10 mMol) chloroacetic acid pyrrolidide are added thereto and the solution maintained for 120 minutes at 100° C. The hot solution is suction filtered from the isoindoline hydrochloride which separates (1.45 g. = 93%), brought to dryness and the residue recrystallised from acetone. There are thus obtained 1.86 g. (81% of theory) β-2-iscindolinyl-acetic acid pyrrolidide with a melting point of 86° C.

Analysis: calc. nitrogen content for $C_{14}H_{18}N_2O$: 12.16%
found : 12.09%

EXAMPLE 4.

β-2-(5-amino-isoindolinyl)-acetamide.

2.68 g. (20 mMol) 5-amino-isoindoline are dissolved in 200 ml. dioxan, 0.94 g. (10 mMol) chloroacetamide are added thereto and the solution heated under reflux. After a few minutes, the separation of 5-amino-isoindoline hydrochloride commences and this separation is completed by boiling the reaction mixture under reflux for 1 hour. The crystals of the hydrochloride are filtered off with suction from the hot solution, 1.45 g. (85% of theory) of this salt being obtained. Upon cooling the filtrate, the desired condensation product separates out as flocculent crystals which are filtered off with suction and recrystallised from dioxan. There are obtained 1.40 g. (72% of theory) β-2-(5-amino-isoindolinyl)-acetamide with a melting point of 211° C.

Analysis: calc. nitrogen content for $C_{10}H_{13}N_3O$: 21.98%
found : 21.94%

EXAMPLE 5.

β-2-(5-amino-isoindolinyl)-acetic acid methylamide.

2.68 g. (20 mMol) 5-amino-isoindoline are dissolved in dioxan, 1.08 g. (10 mMol) chloroacetic acid methylamide are added thereto and the solution heated under reflux for 60 minutes. The hot solution is filtered, evaporated and the residue recrystallised from benzene. There are obtained 1.38 g. (81% of theory) 5-amino-isoindoline hydrochloride and 1.60 g. (78% of theory) β-2-(5-amino-isoindolinyl)-acetic acid methylamide with a melting point of 175° C.

Analysis: calc. nitrogen content for $C_{11}H_{15}N_3O$: 20.47%
found : 20.49%

EXAMPLE 6.

β-2-(5-amino-isoindolinyl)-acetic acid dimethylamide.

2.68 g. (20 mMol) 5-amino-isoindoline are dissolved in benzene, 1.22 g. (10 mMol) chloroacetic acid dimethylamide are added thereto and the solution heated under reflux for 2 hours. The solution is suction filtered, while still hot, from 5-amino-isoindoline hydrochloride (1.57 g. = 92%). Upon cooling, β-2-(5-amino-isoindolinyl)-acetic acid dimethylamide precipitates out and, after recrystallisation from benzene, melts at 123° C. The yield is 1.84 g. (84% of theory).

Analysis: calc. nitrogen content for $C_{12}H_{17}N_3O$: 19.17%
found : 19.15%

EXAMPLE 7.

β-2-isoindolinyl-acetic acid dimethylamide.

9.0 g. (76 mMol) isoindoline and 4.62 g. (38 mMol) chloroacetic acid dimethylamide are dissolved in 100 ml. dioxan and boiled under reflux for 2.5 hours. After removing the precipitated isoindoline hydrochloride, the dioxan is distilled off in a

vacuum, the residue boiled up with the ether and then filtered while still warm. There are obtained 4.7 g. β-2-isoindolinyl-acetic acid dimethylamide (51% of theory) which, after recrystallisation from ether, has a melting point of 58—60° C.

Analysis: calc. nitrogen content for $C_{12}H_{16}N_2O$: 13.71%
found : 13.01%

EXAMPLE 8.

β-2-isoindolinyl-acetic acid ethylamide.

9.5 g. (80 mMol) isoindoline and 4.87 g. (40 mMol) chloroacetic acid ethylamide are dissolved in 75 ml. dioxan and boiled under reflux for 1 hour. The isoindoline hydrochloride formed is filtered off with suction from the hot reaction mixture, the filtrate evaporated to dryness in a vacuum and the residue, after washing with water, recrystallised from benzene. There are obtained 4.33 g. β-2-isoindolinyl-acetic acid ethylamide (53% of theory) which, after recrystallisation from acetone, has a melting point of 130° C.

Analysis: calc. nitrogen content for $C_{12}H_{16}N_2O$: 13.71%
found : 13.24%

EXAMPLE 9.

β-2-isoindolinyl-acetic acid piperidide.

12 g. (0.1 Mol) isoindoline and 8 g. (0.05 Mol) chloroacetic acid piperidide are dissolved in 100 ml. dioxan and left to stand for 30 minutes at room temperature. The separated isoindoline hydrochloride is filtered off with suction and the filtrate boiled under reflux for a further hour. The reaction mixture is again filtered with suction, the filtrate distilled to dryness in a vacuum and the residue stirred with water. The oil which separates is taken up in benzene and the product precipitated therefrom by the addition of petroleum ether. After recrystallisation from ether, there are obtained 4.8 g. β-2-isoindolinyl-acetic acid piperidide (38% of theory) which has a melting point of 54—57° C.

Analysis: calc. nitrogen content for $C_{15}H_{20}N_2O$: 11.47%
found : 11.17%

EXAMPLE 10.

β-2-isoindolinyl-acetic acid morpholinide.

9 g. isoindoline and 6.2 g. chloroacetic acid morpholinide are reacted in a manner analogous to that described in Example 7. There are obtained 5.55 g. β-2-isoindolinyl-acetic acid morpholinide (57% of theory) which, after recrystallisation from ether, has a melting point of 116—118° C.

Analysis: calc. nitrogen content for $C_{14}H_{18}N_2O_2$: 11.37%
found : 11.00%

EXAMPLE 11.

β-2-(5¹-amino-isoindolinyl)-acetic acid ethylamide.

16.1 g. (0.12 Mol) 5-amino-isoindoline and 7.3 g. chloroacetic acid ethylamide are dissolved in 150 ml. dioxan and boiled under reflux for 4 hours. After filtering the 5-amino-isoindoline hydrochloride with suction, the solvent is distilled off from the filtrate in a vacuum, the residue boiled up with benzene, filtered while hot and the filtrate cooled. There are obtained 8.9 g. β-2-(5¹-amino-isoindolinyl)-acetic acid ethylamide (68% of theory) which, after recrystallisation from benzene, melts at 113.5—115° C.

Analysis: calc. nitrogen content for $C_{12}H_{17}N_3O$: 19.17%
found : 19.42%

EXAMPLE 12.

β-2-(5¹-amino-isoindolinyl)-acetic acid piperidide.

9.38 g. (70 mMol) 5-amino-isoindoline and 5.64 g. (35 mMol) chloroacetic acid piperidide are dissolved in 300 ml. dioxan and boiled under reflux for 30 minutes. The 5-amino-isoindoline hydrochloride formed is filtered off from the hot reaction

mixture, the filtrate evaporated to dryness in a vacuum and the residue recrystallised from water. There are obtained 4.6 g. β-2-(5¹-amino-isoindolinyl)-acetic acid piperidide (51% of theory) which melts at 142—143° C. (decomp.).

Analysis: calc. nitrogen content for $C_{15}H_{21}N_3O$: 16.20%
found : 16.17%

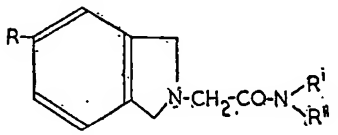
In the following Table there are given the results of pharmacological tests carried out on some of the new compounds according to the present invention and on some known compounds. In this Table, column I gives the toxicity LD_{50} in mg./kg. by interperitoneal injection of mice, column II gives the analgesic effect ED_{50} in mg./kg. by interperitoneal injection of mice, determined by the burning ray method, column III gives the antiphlogistic effect by interperitoneal injection of rats as the liminal dose in mg./kg., determined by the plethysmetric measurement of rat paw oedema induced by dextran and column IV gives the antipyretic effect as the liminal dose by interperitoneal injection in mg./kg. necessary for the suppression of the pyraside fever in rabbits.

TABLE

compound	I	II	III	IV
β-2-isoindolinyl-acetic acid dimethylamide	380	60	10	10
β-2-isoindolinyl-acetic acid ethylamide	300	10	50	20
β-2-isoindolinyl-acetic acid pyrrolidide	210	80	10	20
β-2-isoindolinyl-acetic acid piperidide	270	40	50	50
β-2-isoindolinyl-acetic acid morpholinide	880	15	20	10
β-2-(5¹-amino-isoindolinyl)-acetic acid ethylamide	560	20	50	10
β-2-(5¹-amino-isoindolinyl)-acetic acid piperidide	220	20	100	100
codeine hydrochloride	250	10	—	—
amidopyrine	320	10	100	10
phenylbutazone sodium salt	—	—	100	—

WHAT WE CLAIM IS:—

1. Compounds of the general formula:—



wherein R is a hydrogen atom or a primary amine group and R^1 and R^{11}, which may be the same or different, are hydrogen atoms or alkyl radicals or R^1 and R^{11} may be joined together directly or through a hetero atom to form a cyclic radical; and the acid addition salts thereof with physiologically acceptable acids.

2. β-2-isoindolinyl-acetic acid methylamide.
3. β-2-isoindolinyl-acetic acid methylamide.
4. β-2-isoindolinyl-acetic acid pyrrolidide.
5. β-2-(5-amino-isoindolinyl)-acetamide.
6 β-2-(5-amino-isoindolinyl)-acetic acid methylamide.
7. β-2-(5-amino-isoindolinyl)-acetic acid dimethylamide.
8. β-2-isoindolinyl-acetic acid dimethylamide.
9. β-2-isoindolinyl-acetic acid ethylamide.
10. β-2-isoindolinyl-acetic acid piperidide.
11. β-2-isoindolinyl-acetic acid morpholinide.
12. β-2-(5¹-amino-isoindolinyl)-acetic acid ethylamide.
13. β-2-(5¹-amino-isoindolinyl)-acetic acid piperidide.

14. Process for the preparation of compounds of the general formula given in claim 1, wherein isoindoline or 5-amino-isoindoline is reacted with an appropriate haloacetic acid amide in a solvent.

15. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and with reference to any of the specific Examples.

16. Compounds of the general formula given in claim 1, whenever prepared by the process according to claim 14 or 15.

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